REMARKS

Applicants note with appreciation the Examiner's detailed comments in the Advisory Action. The Applicants respectfully submit that they have already factually demonstrated utility under §101.

Contrary to the position in the rejection, the role of ASICs was not "unknown at the time of filing." The Applicants have already demonstrated that the channels recited in the rejected claims were involved in pain and neurodegeneration. The Applicants' Specification as filed and the additional evidence of record is probative of the asserted utility.

For example, the Applicants have already demonstrated by analogy with prion and Alzheimer disease that even without a known function, the role of protein in a disease can be well established. For ASICs, involvement of ASIC hyperactivity in neurodegeneration can be well established without knowledge of the normal function. Regarding nociception, the Applicants provided evidence that ASIC channels are pain sensors. The rejection apparently discounts these facts and continues to state that the physiological role of ASICs is unknown. This is incorrect.

The rejection also states that there is no association of ASIC channels and disease. The Applicants provided proof that for one skilled in the art the role of ASIC channels in both pain perception and neurodegeneration is evident when reading the Application. Again, the rejection discounts this position. Instead, the rejection states that no association between a disease state and an altered expression level and form of ASIC is known. The Applicants have already established that it is not over-expression, but hyperactivity of ASIC channels that causes neurodegeneration and pain perception.

With respect to the Berdiev paper and the unknown role of ASIC channels in no transformed glia, the Applicants demonstrated that ASIC channels are not expressed in glia, but only in glioma. As indicated above, the unknown role of ASICs in glioma is not relevant to neurodegeneration and pain perception. Again, the rejection discounts these facts.

The Applicants nonetheless submit additional facts to further prove the utility discussed in the Applicants' Specification. Studies in published peer-reviewed journal articles have repeatedly investigated and verified the utility asserted in the Applicants' Specification. For example, the Applicants' assertion of a role in neurodegeneration has been verified by a study that shows that ASIC1a is involved in acidosis-mediated, glutamate-independent, ischaemic

brain injury. The Applicants invite the Examiner's attention to the enclosed article, Pignataro et al., (2007) *Brain*, 130: 151-58. The authors demonstrated that psalmotoxin, a tarantula-derived ASIC1a blocker, has a significant neuro-protective effect on murine models of ischaemic brain injury. Pignataro also demonstrates that ischaemic brain tissue is subject of dynamic changes in pH, which reaches values capable of activating ASIC1a at different phases of injury. The Pignataro study confirms the Applicants' assertions in their Specification that ASICs play a role in neurodegeneration caused by ischaemic and acidic brain injury.

Each of the publications cited in the Advisory Action as allegedly refuting the asserted utility pertain specifically to neurodegeneration in the CNS, but not to the role of ASICs outside of the CNS. Therefore, one skilled in the art would not have looked to these publications as a basis for assessing the role of ASICs outside the CNS, such as those active in pain sensation. As the documents relied upon in the Advisory Action neither refute nor discuss the asserted utility of ASICs in pain sensation, the Applicants respectfully submit that the rejection has not demonstrated that the claimed subject matter lacks utility. While not disclaiming the asserted utility of a role in neurodegeneration, the Applicants respectfully submit that the role of ASICs in pain sensation alone is sufficient to satisfy the requirement of a single credible utility. §101 does not require a long list of different utilities. A single demonstrated utility is sufficient. The Applicants have done that.

Furthermore, several recent post-filing publications confirm the assertions made at filing that ASICs are involved in pain sensation. For example, a recent peer-reviewed publication suggests that ASIC1a "is an important molecular target for treating both acute and neuropathic pain." This is shown in the enclosed Mazzuca et al. (2007) *Nature Neuroscience*. 10(8):943-45 article. The authors observed an anti-nocioceptive effect following the administration of ASIC1a antisense oligodeoxynucleotides and psalmotoxin, thus verifying a specific and significant role of ASIC1a in pain sensation.

Additionally, recent murine knockout studies examine the role of ASIC3 in pain. The first publication measured c-Fos, a marker of neuronal excitation, in the gastritis-induced acid hyperresponsiveness in ASIC2 and ASIC3 knockout mice. This is shown in the enclosed Wultsch et al. (2007) *Pain* article. The Wultsch data indicates that ASIC2-/- mice, unlike ASIC3-/- mice, developed gastric hyperresponssiveness, thus leading the authors to conclude that ASIC3 is "an important target for therapeutic management of hyperalgesia." Another experiment tested

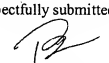
response to mechanical and thermal pain stimuli on ASIC3-knockout mice and mice infected with an ASIC3-vector. This is shown in the enclosed Sluka et al. (2007) *Pain* 129:102-112 article. Sluka demonstrates that ASIC3 is responsible for mechanical hyperalgesia and is critical to the development of hyperalgesia that results from muscle injury.

For the reasons presented above and in the previous Response, the Applicants respectfully submit that there is sufficient evidence presented in the Applicants' Specification for one skilled in the art to accept the role of ASICs in the identified disease pathways and the associated asserted utility. The credibility requirement is assessed by what one skilled in the art would accept as probative of the asserted utility. The Applicants respectfully submit the Specification as filed and the numerous post-filing publications that independently tested and verified the asserted utility factually demonstrate the asserted utility. Consequently, one skilled in the art would consider the asserted utility to be credible and, therefore, the utility requirement is satisfied. Accordingly, withdrawal of the rejection under 35 U.S.C. §101 is respectfully requested.

Claims 1, 11-13, 15, 17-23, 26-27 and 30-31 remain rejected under 35 U.S.C. §112, first paragraph. This rejection follows from and is dependent upon the §101 rejection discussed above. For the reasons set forth above, the Application does, in fact, describe sufficient specific, substantial and credible utilities for the claimed isolated polynucleotide of the ASIC channel. The Applicants, therefore, respectfully request that the §112, first paragraph rejection of Claims 1, 11-13, 15, 17-23, 26-27, and 30-31 be withdrawn.

In light of the foregoing, the Applicants respectfully submit that the Application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,



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